History

- 1844- Claude Bernard. Introduced catheter through carotid artery of a horse into left ventricle to measure temperature.
- 1929- Werner Forsmann. Introduced urologic catheter from brachial vein into right atrium.
History
History

- 1940s - Cournand. Systematic investigation of right heart pressures in normal and diseased hearts.
- 1964 - Dotter. First balloon angioplasty for peripheral artery stenosis.
The age of Intervention

PTCA - 1977
Percutaneous Transluminal Coronary Angioplasty
Mechanism of angioplasty

i. Compression and redistribution of plaque
ii. Embolization of plaque components
iii. Arterial enlargement (aneurysm formation)
iv. Disruption of plaque and arterial wall
v. Intimal tears and dissections
Indication for PTCA according Andreas Gruntzig View

- Proximal stenosis
- Good left ventricular function
- No left main
- No calcified lesion
Indications for PTCA:

- Single vessel disease
- Proximal Lesions

Contraindications:

- Left main, Multivessel, Acute MI, Total occlusion, Bifurcation's, Tortuosity...
There are in general no contraindications

“...The only indication for CABG is a failed PTCA...”
G.Hartzler
A wide variety of balloons
Timeline


Phase 1
- POBA

Phase 2
- Stenting

Phase 3
- Primary Angioplasty for MI

Phase 4
- Brachytherapy

Phase 5
- Drug Eluting stents

You Are Standing Here

---

1970-1999 Timeline with milestones:
- Phase 1: POBA
- Phase 2: Stenting
- Phase 3: Primary Angioplasty for MI
- Phase 4: Brachytherapy
- Phase 5: Drug Eluting stents

The timeline highlights the progression from 1970 to 2010, with each phase representing a significant development in medical technology.
Simpson 1986: Coronary directional atherectomy in humans
Directional Coronary Atherectomy

- Debunking gives Less elastic recoil
- Less dissection
- Wider lumen
- Smoother lumen
Applications of DCA

- Type A lesion in large vessel (> 3mm)
- Severely eccentric lesion
- Abnormal contour (ulceration, flap, limited dissection)
- Ostial lesion
- Large bifurcation lesion
- Moderately lengthy lesion in large vessel
- Salvage for failed PTCA
Auth 1988: rot ablato
Applications for Rotablator

- Calcified lesions
- Tortuous lesions
- Ostial lesions
- Undilatable lesions
- Debulking in Instent restenosis
Coronary Dissections
Sigwart 1986: coronary stenting
Stents

- Better Stent Designs
- Customized Stents
- Bifurcation Stents
- Coated/Covered Stents
- Radioactive Stents
Interventional Cardiology
Technical evolution

Drug-eluting Stent

Modified from Michel Bertrand
Current Problems

- Platelet Activation
- Restenosis
## Restenosis – Data

*Model based on 1555 patients in C-DAC stent trials*

<table>
<thead>
<tr>
<th>Post-Procedure In-Stent MLD</th>
<th>Lesion Length</th>
<th>10 mm</th>
<th>15 mm</th>
<th>20 mm</th>
<th>25 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mm</td>
<td>35%</td>
<td>39%</td>
<td>43%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>3.0 mm</td>
<td>23%</td>
<td>26%</td>
<td>30%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>3.5 mm</td>
<td>15%</td>
<td>17%</td>
<td>19%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>4.0 mm</td>
<td>9%</td>
<td>10%</td>
<td>12%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Diabetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mm</td>
<td>27%</td>
<td>30%</td>
<td>33%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>3.0 mm</td>
<td>17%</td>
<td>19%</td>
<td>22%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>3.5 mm</td>
<td>10%</td>
<td>12%</td>
<td>14%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>4.0 mm</td>
<td>6%</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>
Meta-Analysis
All IIb/IIla Studies
16 studies
32,135 pts
48-96° death

IIb/IIla  Plac.  p
0.20%  0.35%  <0.03
OR 0.70 [0.51, 0.96]

EPIC
EPILOG
RAPPORT
CAPTURE
Simoons
IMPACT I
IMPACT II
IMPACT HiLo
Hopkins
PURSUIT
Kerelakes
RESTORE
PRISM
PRISM+
PARAGON
Theroux
Combined

IIb/IIla better | Placebo better

The platelet was the culprit all along!
In-Stent Restenosis
Compared to Pooled Palmaz-Schatz

MULTI-LINK
PS
NIR
PS
MICRO II
PS
GR II
PS
Odds Ratio
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Serruys, 1998
Closed Cell Design
Closed Cell vs Open Cell Stents
Pharmacological approaches to prevent restenosis

- Antiplatelet and antithrombotic agents
- Anti-inflammatory drugs
- Specific growth factor antagonist
- Antiproliferatives and antineoplastic
- Vasodilators
- Lipid-lowering agents and antioxidants
- Local drug delivery and molecular strategies
**Radiation Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Dose (Gy)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRIST</td>
<td>$^{192}\text{Ir}$</td>
<td>15</td>
<td>130</td>
</tr>
<tr>
<td>SVG-WRIST</td>
<td>$^{192}\text{Ir}$</td>
<td>15-18</td>
<td>120</td>
</tr>
<tr>
<td>Long WRIST</td>
<td>$^{192}\text{Ir}$</td>
<td>15-18</td>
<td>120</td>
</tr>
<tr>
<td>GAMMA-1</td>
<td>$^{192}\text{Ir}$</td>
<td>8-30</td>
<td>250</td>
</tr>
<tr>
<td>ARTISTIC</td>
<td>$^{192}\text{Ir}$</td>
<td>12-18</td>
<td>290</td>
</tr>
<tr>
<td>Beta-WRIST</td>
<td>$^{90}\text{Y}$</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>INHIBIT</td>
<td>$^{32}\text{P}$</td>
<td>20</td>
<td>330</td>
</tr>
<tr>
<td>START</td>
<td>$^{90}\text{Sr/Y}$</td>
<td>20</td>
<td>390</td>
</tr>
</tbody>
</table>
In-Stent Restenosis
Sirolimus (Rapamycin)

- A naturally occurring antimicrobial first found on Easter Island
- Potent immunosuppressive activity
- Developed and marketed by Wyeth Ayerst Labs for prevention of renal transplant rejection (Rapamune®)*
- Novel inhibitor of growth factor & cytokine-stimulated cell proliferation
- Mechanism of action: cell-cycle inhibition

*Rapamune is a registered trademark of Wyeth Ayerst.
Histology of Sirolimus stent

3 days

Control  Sirolimus-coated

30 days
The DES Revolution
Paclitaxel
Components of the Endeavor Stent

- Cobalt Alloy
- Modular stent
- Strut thickness 0.0036"
- Biocompatible PC Technology (phosphorylcholine polymer)
- Delivery based on discrete, secure Technology
- ABT-578 (Sirolimus analogue) 10 µg/mm stent dosage
SIRIUS Clinical Data:
Odds Ratio for TLR by Subgroup at 9 Months

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sirolimus</th>
<th>Control</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
<th># events prevented per 1,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4.1</td>
<td>16.6</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>124</td>
</tr>
<tr>
<td>Male</td>
<td>4.4</td>
<td>16.6</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>122</td>
</tr>
<tr>
<td>Female</td>
<td>3.4</td>
<td>16.5</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0007</td>
<td>130</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.9</td>
<td>22.3</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0006</td>
<td>154</td>
</tr>
<tr>
<td>No Diabetes</td>
<td>3.2</td>
<td>14.3</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>111</td>
</tr>
<tr>
<td>LAD</td>
<td>5.1</td>
<td>19.8</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>147</td>
</tr>
<tr>
<td>Non-LAD</td>
<td>3.4</td>
<td>14.3</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>109</td>
</tr>
<tr>
<td>Small Vessel (&lt;2.75)</td>
<td>6.3</td>
<td>18.7</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>125</td>
</tr>
<tr>
<td>Large Vessel</td>
<td>1.9</td>
<td>14.8</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>128</td>
</tr>
<tr>
<td>Short Lesion</td>
<td>3.2</td>
<td>16.1</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>129</td>
</tr>
<tr>
<td>Long Lesion (&gt;13.5)</td>
<td>5.2</td>
<td>17.4</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>122</td>
</tr>
<tr>
<td>Overlap</td>
<td>4.5</td>
<td>17.7</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0003</td>
<td>131</td>
</tr>
<tr>
<td>No Overlap</td>
<td>3.9</td>
<td>16.1</td>
<td>1.0</td>
<td>0.9-0.8</td>
<td>0.0001</td>
<td>121</td>
</tr>
</tbody>
</table>

TAXUS IV Clinical Data: Odds Ratio for TLR by Subgroup at 9 Months

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Taxus™</th>
<th>Control</th>
<th>P value</th>
<th># events prevented per 1,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.0</td>
<td>11.3</td>
<td>&lt;0.0001</td>
<td>83</td>
</tr>
<tr>
<td>Diabetes - oral</td>
<td>4.8</td>
<td>17.4</td>
<td>0.004</td>
<td>126</td>
</tr>
<tr>
<td>Diabetes - insulin</td>
<td>5.9</td>
<td>13.0</td>
<td>0.32</td>
<td>71</td>
</tr>
<tr>
<td>No Diabetes</td>
<td>2.4</td>
<td>9.8</td>
<td>&lt;0.0001</td>
<td>74</td>
</tr>
<tr>
<td>LAD</td>
<td>3.4</td>
<td>13.4</td>
<td>&lt;0.0001</td>
<td>100</td>
</tr>
<tr>
<td>Non LAD</td>
<td>2.8</td>
<td>9.7</td>
<td>0.0001</td>
<td>69</td>
</tr>
<tr>
<td>RVD &lt;2.5</td>
<td>3.4</td>
<td>15.4</td>
<td>&lt;0.0001</td>
<td>120</td>
</tr>
<tr>
<td>RVD &gt;3.0</td>
<td>2.5</td>
<td>6.7</td>
<td>0.057</td>
<td>42</td>
</tr>
<tr>
<td>Lesion &gt;20 mm</td>
<td>3.3</td>
<td>18.6</td>
<td>0.0001</td>
<td>153</td>
</tr>
<tr>
<td>Lesion &lt;10 mm</td>
<td>3.3</td>
<td>9.3</td>
<td>0.01</td>
<td>60</td>
</tr>
</tbody>
</table>

**ENDEAVOR II**

TLR-Free Survival at 360 Days

- **94.0%**
- **86.9%**
- *p* < 0.001, log rank

(Event Free ±1.5 SE)

![Graph showing TLR-Free Survival over time for ENDEAVOR II trial. The graph compares the freedom from TLR events between DRIVER and ENDEAVOR cohorts over time. The x-axis represents time after the initial procedure in days, ranging from 0 to 360. The y-axis represents the freedom from TLR, ranging from 0% to 100%. The lines show a decrease in freedom from TLR over time, with ENDEAVOR showing a higher percentage of TLR-free survival compared to DRIVER at 360 days.]
To DES or not to DES?
DES Penetration in the United States: Dominant Technology

Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4  Q3
2003 2004 2005

0 19 41 47 56 77 83 87 91%


Cypher approved April 2003 and Taxus approved March 2004
Choice of DES: Release Kinetics

- ENDEAVOR™
- CYPHER™
- ML VISION® DES
- CHAMPION™
- BIOMATRIX™ (BA9)
- TAXUS™

Cumulative % released vs Days
Stent Re-endothelialization @ 14 d. Rabbit Iliac

Data on file at Abbott Vascular
Late Loss & TLR Vs. Stent Type

Mauri et al.
Circ 2005

$r^2=0.22$
$y = 9.28x + 3.41$
$p<0.001$
Late Loss and stent type

Mauri et al. Circulation 2005

Adjusted to DM and lesion length
## Choice of Stent

<table>
<thead>
<tr>
<th>CYPHER Sirolimus-eluting Stent</th>
<th>TAXUS paclitaxel-eluting stent</th>
<th>ENDEAVOR ABT-578 eluting Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 ( \mu )g/cm(^2) sirolimus</td>
<td>100 ( \mu )g/cm(^2) paclitaxel</td>
<td>ABT-578</td>
</tr>
<tr>
<td>Cytostatic MoA antiproliferative and anti-inflammatory action</td>
<td>Cytotoxic MoA antiproliferative effect</td>
<td>Sirolimus analogue</td>
</tr>
<tr>
<td>Released from closed-cell stent system</td>
<td>Closed-cell stent system</td>
<td>Open cell system</td>
</tr>
</tbody>
</table>
### RCTs Comparing Cypher to Taxus

<table>
<thead>
<tr>
<th></th>
<th>TAXI</th>
<th>REALITY</th>
<th>SIRTAX</th>
<th>ISAR-Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>not defined</td>
<td>Cypher superior</td>
<td>Cypher superior</td>
<td>non-inferior</td>
</tr>
<tr>
<td>Multicenter</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Clinical primary endpoint</td>
<td>n/a</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>n/a</td>
<td>angiographic</td>
<td>clinical</td>
<td>angiographic</td>
</tr>
<tr>
<td>Time of PE</td>
<td>6 months</td>
<td>8 months</td>
<td>9 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Parameter</td>
<td>n/a</td>
<td>in lesion RR</td>
<td>MACE</td>
<td>in-segment LLL</td>
</tr>
<tr>
<td>Patients</td>
<td>102/100</td>
<td>684/669</td>
<td>503/509</td>
<td>125/125</td>
</tr>
<tr>
<td>Lesion length</td>
<td>not mentioned</td>
<td>(17.0/17.3)10&lt;;15&lt;</td>
<td>&quot;all&quot;(12.4/13.4)</td>
<td>13.8/12.4</td>
</tr>
<tr>
<td>Vessel diameter</td>
<td>(3.2/3.2)</td>
<td>(2.4/2.4)3.0–2.25</td>
<td>(2.8/2.8)4.0–2.25</td>
<td>2.7/2.8</td>
</tr>
<tr>
<td>Restenosis in Segment</td>
<td>n/a</td>
<td>9.6/11.1</td>
<td>*6.7/11.9</td>
<td>*6.9/16.5</td>
</tr>
<tr>
<td>Late lumen Loss in Stent</td>
<td>n/a</td>
<td>*0.09/0.31</td>
<td>*0.13/0.25</td>
<td>*0.43/0.67</td>
</tr>
<tr>
<td>TVR</td>
<td>2.0/1.0</td>
<td>1.6/1.2</td>
<td>*6.0/9.2</td>
<td>6.4/12.2TLR</td>
</tr>
<tr>
<td>MACE</td>
<td>6.0/4.0</td>
<td>9.2/10.8</td>
<td>*6.2/10.8</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint reached</td>
<td>n/a</td>
<td>no</td>
<td>yes</td>
<td>No; in Seg LL(0.19/0.46)</td>
</tr>
<tr>
<td>Major limitation</td>
<td>no primary endpoint</td>
<td>no clinical primary endpoint</td>
<td>no multicenter trial</td>
<td>no clinical primary endpoint</td>
</tr>
</tbody>
</table>

The only study reaching the primary endpoint was SIRTAX, but it was not a multicenter study. There is no randomized, controlled multicenter trial with a primary clinical endpoint and adequate power showing that one DES is superior to another.
Freedom from TLR

RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS (n=1,748)

- Bare-Metal Stent
- CYPHER®

93.6% 76.8%

P<0.0001

TAXUS II, IV, V, VI (n=3,445)

- Bare-Metal Stent
- TAXUS®

90.6% 80.1%

p<0.0001

Time after Initial Procedure (months)
Freedom from Cardiac Death

RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS (n=1,748)
98.2%
97.8%
P=0.61

TAXUS II, IV, V, VI (n=3,445)
98.0%
97.9%
P=0.81

Bare-Metal Stent
CYPHER®

Bare-Metal Stent
TAXUS®

Time after Initial Procedure (months)
Bare Metal Stent in Proximal RCA and SRL-Eluting Stent in Distal RCA 15 Months Antemortem (Non-Cardiac Death)

SRL-Eluting

Bare Metal Stent

Joner M. JACC 2006;48:193–202
The Biolimus A9 Stent

Biolimus A9
- potent
- cytostatic
- anti-prolif/inflamm

BA9 Stent

Biosensors open cell S stent

Bioabsorbable PLA polymer composite
Nobori DES Components

**S-Stent™ (stainless steel)**
- Quadrature-link design
- Excellent flexibility and scaffolding
- Reduced turbulence and wall injury

**PLA bioabsorbable Polymer**
- High drug-carrying capacity
- Controlled biodegradability
- Simultaneous polymer degradation and release of drug into tissue
- Abluminal Coating

**Biolimus A9™ (rapamycin derivative)**
- A potent new “Limus” designed for stent applications
- Powerful immunosuppressant, anti-inflammatory compound
- Prevents smooth muscle cell proliferation
- Highly lipophilic; elutes fast from stent
New Stents: Everolimus eluting stents

Guidant XIENCE V DES

- Everolimus
- Durable Polymer Control Release
- ML VISION® Stent Platform
- ML VISION® Stent Delivery System

Coating Thickness (OD)

<table>
<thead>
<tr>
<th></th>
<th>CYPHER®</th>
<th>TAXUS®</th>
<th>XIENCE™ V</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2 µm</td>
<td>15.6 µm</td>
<td>5.3 µm</td>
<td></td>
</tr>
</tbody>
</table>
New Stents: Microporous

- Yukon (Translumina)

Before

After
BioMatrix™ Stent Components
(Biosensors International Group)

S-Stent™ (stainless steel)
- Quadrature-link design; increased flexibility
- Excellent scaffolding
- Reduced turbulence and wall injury

PLA Polymer
- Uniform thickness; bioresorbable
- Simultaneously releases drug and polymer
- Controlled biodegradability
- High drug-carrying capacity
- Minimizes polymer weight to minimize inflammation; polymer absorbed into tissue

Biolimus A9™ (rapamycin derivative)
- Powerful immunosuppressant, anti-inflammatory
- Prevents smooth muscle cell proliferation
- More lipophilic; elutes faster than rapamycin
### New stents: Bioabsorbable

<table>
<thead>
<tr>
<th>Stent</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igaki-Tamai</td>
<td>PLA</td>
</tr>
<tr>
<td>BVS</td>
<td>PLA</td>
</tr>
<tr>
<td>Sahajanand</td>
<td>PLA</td>
</tr>
<tr>
<td>REVA</td>
<td>Tyrosine-Policarbonate</td>
</tr>
<tr>
<td>BIT</td>
<td>PAE-Salicylate Magnesium</td>
</tr>
<tr>
<td>Biotronik</td>
<td></td>
</tr>
</tbody>
</table>
BVS bioabsorbable stent
An absorbable metallic magnesium alloy stent
New Stents: EPC surface capture

GENOUS: the Role of Endothelial Progenitor Cells (EPCs)

1) EPCs originate from bone marrow
2) EPCs circulate through the bloodstream
3) EPCs are captured by antibodies immobilized on the stent surface
4) Endothelial layer is rapidly formed over and between the stent struts

© Orbus MT Inc.
EPC capture: 1h.
Dedicated Bifurcation Stents

AST petal
Guidant frontier
YMed sidekick

Devax (+ BA9)
“true” bifurcation designs
sidebranch designs
Dedicated small vessel stent

A guidewire based platform technology for delivery and deployment of stents to small vessels and tortuous vascular anatomy.
“..There are costs and risks to a program of action but they are far less than the long-range costs and risks of comfortable inaction.”

J.F.K